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EXAMINER	
BAKER, A	
ART UNIT	**PAPER NUMBER**
1632	36

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/486,313	Applicant(s) Weiss et al.
	Examiner Anne-Marie Baker, Ph.D.	Group Art Unit 1632

☒ Responsive to communication(s) filed on *Jul 21, 1999*.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *26, 27, 32-37, and 39-62* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *26, 27, 32-37, and 39-62* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

The amendment filed July 21, 1999 (Paper No. 35) has been entered. Claims 34 and 40 have been amended. Claims 60-62 have been newly added.

Claims 26, 27, 32-37, and 39-62 are pending in the instant application.

The following rejections are reiterated and constitute the complete set of rejections being applied to the instant application. Rejections and objections not reiterated from the previous office action are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26, 27, 32-37, and 39-62 stand and are rejected under 35 U.S.C. 112, first paragraph for reasons of record advanced in the previous Office Action mailed 1/21/99 (Paper No. 29).

The claims are directed to methods of transplanting neural stem cell progeny into a host by obtaining a population of cells derived from mammalian neural tissue containing at least one multipotent CNS neural stem cell, where the neural stem cell produces progeny that differentiate into neurons that express neuron specific enolase or neurofilament and glia that express glial fibrillary acidic protein or galactocerebroside; culturing the neural stem cells in a culture medium containing one or more growth factors that induce multipotent neural stem cell proliferation; inducing proliferation of multipotent neural stem cells to produce

progeny which includes multipotent neural stem cell progeny cells and transplanting said multipotent neural stem cell progeny into the host.

The claims are not enabled because the transplantation of multipotent neural stem cell progeny into a host has not been demonstrated to provide any therapeutic benefit to the host. The specification clearly teaches that the use for the transplant method is to produce a therapeutic effect in the host.

Applicants argue that the claims recite a method of transplanting CNS neural stem cells to a host and that the Examiner has improperly read limitations from the specification into the claims. However, the specification must teach one skilled in the art not only how to perform the claimed method but also how to use the claimed method. The instant specification teaches only that the methods of transplantation can be used to provide therapeutic benefit to the host.

Applicants argue that one skilled in the art could have readily transplanted the CNS neural stem cells of the invention, without undue experimentation, by using the specification as a guide. However, nowhere in the specification are any transplantation methods taught that result in a therapeutic effect. Thus the specification does not teach how to use the disclosed methods.

Applicants argue that the specification teaches a non-therapeutic transplantation utility in that it teaches that transformed CNS neural stem cells transplanted into a host produce β-galactosidase in the host. Applicants refer to p. 78, Example 27 for providing the non-therapeutic utility of determining neural development events. However, the specification does not assert any such non-therapeutic utility. The passage that Applicants point to merely describes an experiment demonstrating the *in vivo* proliferation of neural stem cells. The example does not involve the transplantation of neural stem cells, but rather only involves the administration of a recombinant retrovirus and several growth factors.

Applicants argue that the specification teaches and provides working examples of transplantation and remyelination. Applicants further argue that demonstration of partial remyelination is evidence of an enabled method of transplantation. However, the specification does not teach a method of transplantation that produces a therapeutic effect and the specification does not teach any other use for the method of transplantation. Thus, evidence of remyelination is not considered enabling for the claimed method because the remyelination was not sufficient to produce a therapeutic effect. The specification does not teach any benefit to using the method to produce partial remyelination. Applicants offer additional evidence of remyelination in rodents and dogs, but no therapeutic effect is demonstrated.

Applicants offer the McKay review article as evidence that neural cell transplantation was enabled at the time of filing. Applicants state that McKay further teaches that transplantation of CNS neural stem cells into a host had been done by 1997, using methods similar to the methods described in the specification. However, the methods described in the specification have not, in fact, been used to produce any therapeutic effect and Applicants have not taught how to use the claimed method for anything else.

Applicants argue, on pages 6-8 of the response, that they have shown transplantation of both mouse and human CNS neural stem cells. Applicants point out the many advantages that the cells of the present invention can provide when used for transplantation, e.g. that they are capable of giving rise to neuronal and glial cells throughout the life span of the organism. Applicants further assert that because CNS neural stem cells "appear to make appropriate lineage decisions when transplanted into a mutant environment, they may provide an excellent source of cells for a variety of future therapies using cellular transplantation." The various characteristics of the cells of the invention and their potential for use in therapeutic transplantation does not further support the Applicants claim that the methods of transplantation were enabled at the time of filing. While the specification teaches several protocols for transplanting the cells of the invention, the

specification does not teach how to use the claimed methods to produce a therapeutic effect. The characteristics of the cells used in the claimed methods cannot make up for this deficiency.

Applicants argue that others skilled in the art have confirmed the suitability of human CNS neural stem cells for transplantation. Applicants point to Cattaneo et al. (1996) for its statement that human CNS neural stem cells are "a plentiful source of neurons and glia suitable for transplantation." The putative suitability of the cells of the invention for transplantation is not sufficient to enable the methods of the invention because the methods of transplantation must be taught in the specification so that one skilled in the art can use the method to do that which the specification itself teaches should result from application of the method, and that is to produce a therapeutic effect. Applicants have not addressed this issue.

Applicants argue that others have used the methods of the invention to show that transplantation of canine CNS neural stem cells results in remyelination in dogs. Applicants point to the publication of Milward et al. (1997). However, Milward et al. does not demonstrate application of the claimed method to produce a therapeutic effect.

Applicants argue that others have used the claimed methods to show transplantation of mouse CNS neural stem cells and incorporation of differentiated glial cells in rat brains. Applicants point out that Winkler et al. (1998) showed that CNS neural stem cells can respond to host-derived environmental cues, differentiate into cells with neuronal and glial-like features, and become integrated in the developing recipient brain. However, this reference does not provide evidence that the claimed methods can be used to produce a therapeutic effect. In the absence of appropriate guidance, one skilled in the art would not know how to use the claimed method to produce a therapeutic effect.

Applicants argue that others have used the claimed methods of the invention for therapeutically effective transplantation of human CNS neural stem cells into mice. Applicants offer several references in

support of this claim, but none of the references (Zigova and Sanberg, 1998; Flax et al., 1998; and Brustle et al., 1998) describe a therapeutic benefit to the mice upon transplantation. The references only demonstrate that human CNS neural stem cells can differentiate into functional neural cells *in vivo* in mice.

Applicants argue that others have used the claimed methods to produce "robust remyelination." Applicants further argue that others have used the claimed methods to produce global cell replacement and therapeutically effective remyelination in mice. While some therapeutic effect was seen, in so far as a number recipient animals showed a decline in symptomatic tremor, it is not evident that the neural stem cell clone (p. 7030, column 1, paragraph 3) used in the experiment was derived in the same manner as is taught in the instant specification. Thus, it does not support enablement for the claimed methods.

Applicants argue that others have used the claimed methods to show that transplantation of CNS neural stem cells results in site-specific migration and neuronal differentiation of human neural progenitor cells after transplantation in the adult rat brain. Applicants point to the work of Fricker et al. (1999) which describes substantial migration of CNS neural stem cells. However, the *in vivo* behavior of CNS neural stem cells is not sufficient evidence to enable the methods of the invention, as the methods of the invention are clearly intended to provide a therapeutic benefit as evidenced by the specification.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 34, 61, and 62 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 34 is indefinite for the use of improper Markush language.

Claims 61 and 62 are indefinite because "the composition of claim 60" lacks antecedent basis. Claim 60 is directed to a method.

Conclusion

No claim is allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Since the fee set forth in 37 CFR 1.17(r) for a first submission subsequent to a final rejection has been previously paid, applicant, under 37 CFR 1.129(a), is entitled to have a second submission entered and considered on the merits if, prior to abandonment, the second submission and the fee set forth in 37 CFR 1.17(r) are filed prior to the filing of an appeal brief under 37 CFR 1.192. Upon the timely filing of a second submission and the appropriate fee of $770 for a large entity under 37 CFR 1.17(r), the finality of the previous Office action will be withdrawn. If a notice of appeal and the appeal fee set forth in 37 CFR 1.17(e)

were filed prior to or with the payment of the fee set forth in 37 CFR 1.17(r), the payment of the fee set forth in 37 CFR 1.17(r) by applicant will be construed as a request to dismiss the appeal and to continue prosecution under 37 CFR 1.129(a). In view of 35 U.S.C. 132, no amendment considered as a result of payment of the fee set forth in 37 CFR 1.17(r) may introduce new matter into the disclosure of the application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Baker whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Friday from 8:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian Stanton, can be reached on (703) 308-2801. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Anne-Marie Baker, Ph.D.

Bruce Campell

BRUCE R. CAMPELL
PRIMARY EXAMINER
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